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10/510,698	10/08/2004	**Kurt Berlin**		4311

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EXAMINER	
STAPLES, MARK	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,698	BERLIN, KURT	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11,15-18 and 25-30* is/are pending in the application.

4a) Of the above claim(s) *25-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/07/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment of claims 8 and 15-18 and the cancellation of claims 1-7, 12-14, and 19-24 in the paper filed on 06/23/2008 is acknowledged.

Claims 8-11 and 15-18 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections that are Withdrawn

Priority

2. It is acknowledged that Applicant has inserted a proper reference in the first sentence of the specification to prior Application No. 60/370,690 as well as to PCT/ICB03/01791.

Information Disclosure Statement

3. It is acknowledged that Applicant has submitted an Information Disclosure Statement. Documents submitted in English have been considered.

Oath/Declaration

4. It is acknowledged that Applicant has submitted a Declaration with the inventor's signature and date of signature.

Specification

5. The objection to improper use of trademarks is withdrawn in light of Applicant's amendment of the specification to properly indicate trademarks.

Canceled Claim Objections and Rejections Moot / Withdrawn

6. The objections and rejections of cancelled claims 1-7, 12-14, and 19-24 are moot and therefore are withdrawn.

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

7. The rejection of claim 18 under 35 USC § 112 Second Paragraph is withdrawn in light of Applicant's amendments to overcome this rejection.

Claim Rejections Withdrawn - 35 USC § 102(b)

8. The rejection of claims 7-10 and 15-17 under 35 U.S.C. 102(b) as being anticipated by Eads et al. (2000) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection which are necessitated by claim amendment.

Canceled Claim Rejections Moot / Withdrawn - 35 USC § 102(e)

9. The rejection of cancelled claims 1-6 under 35 U.S.C. 102(e) as being anticipated by Olek et al. (US Patent No. 6,214,556, issued April 10, 2001, filed on September 22, 1999) is moot and therefore is withdrawn.

10. The rejection of canceled claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Olek et al. (WO 2002/002809, filed on 02 July 2001, in English and designating the US) is moot and therefore is withdrawn.

Claim Rejections Withdrawn - 35 USC § 103(a)

11. The rejections of claims 11 and 18 under 35 U.S.C. 103(a) as being unpatentable over Eads et al., and further in view of Olek et al. (1999) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection which are necessitated by claim amendment.

12. The rejections of claims 11 and 18 under 35 U.S.C. 103(a) as being unpatentable over Eads et al., and further in view of Olek et al. (WO 2002/002809, published 10 January 2002) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection which are necessitated by claim amendment.

Double Patenting Rejection Withdrawn

13. The provisional rejection of claims 8-11 and 15-18 is withdrawn on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/493,727. Claims 1-7, 12-14, and 19-24 are canceled and thus the rejection is moot for these claims and therefore is withdrawn. Regarding

claims 8-11 and 15-18, Applicant arguments and in view of the claim amendments are persuasive.

New Rejections Necessitated by Amendment

Specification

14. The amendment by deletion of the last sentence on page 3 of *Amendments to the Specification* filed 11/07/2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The amended material which is not supported by the original disclosure is as follows: by deletion of this sentence Applicant is introducing new matter by broadening the scope of methylation specific primers (MSP primers).

Applicant is required to remove the new matter by canceling the deletion and reinstating the original sentence in the reply to this Office Action.

Claim Rejections - 35 USC § 103

15. Claims 8-10 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laird et al. (cited on the IDS, United States Patent 6,331,393 filed May 14, 1999 and issued December 18, 2001), Honess et al (1989), and Griswold et al. (2001).

Regarding claim 8, Laird et al. teach methods for the analysis of the methylation status of one or more CpG dinucleotides within a nucleic acid sample (entire Patent, see for example the Abstract), comprising:

a. in the nucleic acid sample, converting cytosine bases that are unmethylated at the 5-position by treatment with a converting agent to uracil or another base which is dissimilar to cytosine in terms of base pairing behavior (see claim 1 step a and claim 7 step a);

b. amplifying one or more nucleic acids of the treated nucleic acid in a polymerase enzyme reaction (see claim 1 step b and claim 7 step b) by means of at least two three primer oligonucleotide pairs (see column 17 line 54 to column 18 line 19), wherein one primer pair does not contain a CpG dinucleotide and does not contain a TpG dinucleotide by teaching:

> "The forward and reverse primer sets used for the MLH1 and CDKN2A genes are:
> GGAGGTTATAAGAGTAGGGTTAA [SEQ ID NO. 41],
>
> CCAACCAATAAAAACAAAAATACC [SEQ ID NO. 42] (MLH1 promoter) . . . "
>
> which is primer pair not containing a CpG and not containing a TpG,

and the other primer pairs are methylation specific primers, and further wherein the amplificates formed from each species of primer pairs differ respectively in at least one of length, sequence, and a detectable label selected from the group consisting of fluorescence labels, mass labels, and radioactive labels by teaching fluorescence label moieties (see claims 5 and 11);

c. detecting the amplificates formed from the primer pairs (see claim 1 step c and claim 7 step c);

d. measuring the amounts of the amplificates formed from each primer pair (see claim 13); and

e. determining the degree of methylation at each analyzed CpG position from ratios of amplificates formed from each of said methylation specific primers relative to amplificates formed from said primer pair that amplifies said reference sequence by teaching:

> "Thus, in its most simple form, the inventive process can be performed by designing reactions for the fully methylated and the fully unmethylated variants that represent the most extreme sequence variants in a hypothetical example (see FIG. 3, Application D). The ratio between these two reactions, or alternatively the ratio between the methylated reaction and a control reaction (FIG. 3, Application A), would provide a measure for the level of DNA methylation at this locus" (see column 15 lines 11-16).

Further regarding claim 1, Laird et al. specifically teach primer oligonucleotide pairs, wherein one primer pair does not contain a CpG dinucleotide : "Primers . . . were also designed for a stretch of the MYOD1 gene (Myogenic Differentiation Gene), completely devoid of CpG dinucleotides as a control reaction for the amount of input DNA" (see column 18 lines 32-35).

Regarding claim 1, Laird et al. specifically teach a primer pair wherein one primer pair does not contain a CpG dinucleotide and does not contain a TpG dinucleotide as noted above but do not specfically teach that this primer pair " . . . amplifies a reference sequence ".

Regarding claim 9, Laird et al. teach where the converting agent is bisulfite (see sentence 2 of the Abstract).

Regarding claim 10, Laird et al. teach where the amplificate is detected by a real time fluorescent system (see last sentence in Fig 4 description in column 8).

Regarding claim 15, Laird et al. teach where Methylation Specific Primers (MSP which are not reference primers) include CpG (see column 4 line 58 to column 5 line 13).

Regarding claim 16, Laird et al. teach where amplificates synthesized/amplified with from each MSPpair is compared to those from other MSP pair and teach where amplificates from a MSP pair are compared to control amplificates from control primers (non-MSP, see column 15 lines 11-16).

Regarding claim 17, Laird et al. teach where the degree of methylation is carried out by determining the amount of methlyation by MSP pairs compared to the non-methlyated amplificate from the control/reference primer pair (see column 15 lines 11-16).

Regarding claim 18, Laird et al. teach where the amplificates are modified by alkylation which is methylation (see sentence 2 of the Abstract).

Regarding claim 8, Griswold et al. teach that partial demethylation of a CpG site will result in a TpG site, that is, that a TpG site will be substituted for a CpG (see last sentence in Figure 7).

Regarding claim 8, Honess et al. teach that deamination of a CpG site will result in a TpG site, that is, that a TpG site will be substituted for a CpG (see 1st full sentence on p. 843).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Laird et al. by using a reference primer pair which does not contain a CpG and does not contain a TpG as suggested by Laird et al., Griswold et al., and Honess et al. with a reasonable expectation of success. The motivation to do so is provided by Laird et al. who teach MSP pairs (a type of primer pair) which do not contain either a CpG nor a TpG and teach that this MSP pair can be substituted for a reference primer pair (see column 15 lines 11-16) to determine methylation status by ratio comparisons. Further motivation is provided by Griswold et al. and Honess who each teach that a TpG will be substituted for a CpG by partial methylation and deamination respectively. Thus to avoid measurement with a reference primer pair of CpG actually present, or formerly present but now represented by TpG; Laird et al., Griswold et al., and Honess et al. teach that not only would CpG need to be absent but TpG would need to be absent as well in the reference primer pair. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

16. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Laird et al., Griswold et al., and Honess et al. as applied to claims 8 and 10 above, and further in view of Olek et al. (1999, previously cited).

Laird et al., Griswold et al., and Honess et al teach as noted above.

Laird et al., Griswold et al., and Honess et al do not specifically teach mass spectrometry, either MALDI or ESI, and do not specifically teach PNA oligonucleotides.

Regarding claim 11, and 23, Olek et al. (1999) teach methods of detecting the amplificates by means of mass spectrometry including MALDI and ESI (see claim 16 and see column 23 lines 31-35) including oligonucleotides which are modified by substitutions with PNA nucleotides (see column 17, lines 21-22).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Laird et al., Griswold et al., and Honess et al. by using PNA nucleotides and detection by MALDI or ESI as suggested by Olek et al. (1999) with a reasonable expectation of success. The motivation to do so is provided by provided by Olek et al. (1999) who teach: "Furthermore, the scope of protection should also include oligonucleotides used as amplification primers, which are used within the overall concept of the method . . . such as, for example, oligonucleotides based on PNA (protein-nucleic acid), chemically modified oligonucleotides: and modified or unmodified oligonucleotide . . ." (see column 17 line 15-24) and: "A variant of the method was developed which allows the detection of very large numbers of cytosines and/or guanines in bisulfite-treated DNA by mass spectrometric measurement of lengths in mass spectrometers based on MALDI" (see

column 20 lines 58-61). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

17. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Laird et al., Griswold et al., and Honess et al. as applied to claims 8 and 10 above, and further in view of Olek et al. (WO 2002/002809, published 10 January 2002, previously cited).

Laird et al., Griswold et al., and Honess et al teach as noted above.

Laird et al., Griswold et al., and Honess et al do not specifically teach mass spectrometry, either MALDI or ESI, and do not specifically teach PNA oligonucleotides.

Regarding claim 11, and 23, Olek et al. (Jan. 2002) teach methods of detecting the amplificates by means of mass spectrometry, including MALDi or ESI (see claim 27) and oligomers which are modified by substitutions with PNA nucleotides (see Abstract and claim 16).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Laird et al., Griswold et al., and Honess by using PNA nucleotides and detection by MALDI or ESI as suggested by Olek et al. (Jan. 2002) with a reasonable expectation of success. The motivation to do so is provided by Olek et al. (Jan. 2002) who teach " . . . PNA-oligomers for detecting the cytosine methylation state of genes . . ." (see Abstract). Further motivation is provided by Olek et al. (Jan. 2002) who teach: "Matrix Assisted Laser Desorption Ionization Mass Spectrometry (MALDI-TOF) is a very efficient development for the analysis of biomolecules" (see p. 5, 1st sentence of 3rd parargraph)

and " . . . detection may be carried out and visualized by means of matrix assisted laser desorptionlionization mass spectrometry (MALDI) or using electron spray mass spectrometry (ESI)" (see p. 10, last sentence of 3rd pargraph). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

18. No claim is free of the prior art.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
September 27, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637